Digestive and Liver Disease 42 (2010) 92–98

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Autoimmune pancreatitis: A challenging diagnostic puzzle for clinicians

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ARTICLE INFO

Article history:
Received 1 August 2009
Accepted 27 August 2009
Available online 4 October 2009

Keywords:
Pancreatitis
Autoimmune
Pancreatic biopsy
Pancreatic imaging

ABSTRACT

Autoimmune pancreatitis is a form of pancreatitis with autoimmune stigmata that may present as either focal or diffuse gland involvement. In focal forms, autoimmune pancreatitis shares demographic, clinical, biochemical and imaging features with pancreatic cancer. Since autoimmune pancreatitis is a benign disease and steroid therapy can rapidly resolve symptoms, improve radiological findings and avoid unnecessary surgery, the current clinical challenge is how to differentiate autoimmune pancreatitis from pancreatic neoplasia.

Even though definitive diagnosis of the disease is difficult, several diagnostic criteria have been proposed and progress has been made in imaging studies. The management of this unique form of pancreatitis should, therefore, be handled in centres with knowledge of all aspects of the disease.

This article briefly reviews clinical aspects of autoimmune pancreatitis with a focus on its diagnostic imaging and management.

1. Introduction

Autoimmune pancreatitis (AIP) is a form of pancreatitis with clinical, serological and histological features of an autoimmune process.

The term AIP (proposed by Yoshida in 1995 [1]) replaced older designations whose diversity reflects the heterogeneity of this disease: primary chronic pancreatitis [2], chronic sclerosing pancreatitis, non-alcoholic duct-destructive chronic pancreatitis [3], lymphoplasmacytic sclerosing pancreatitis [4,5] and duct-narrowing chronic pancreatitis [6].

The first descriptions of AIP from Asian studies included only diffuse forms of the disease that involved the entire gland [7,8]. A diffuse narrowing of the main pancreatic duct was in fact "mandatory" in the Japanese diagnostic criteria of AIP [7,8], and a diffuse enlargement of the pancreas with narrowing of the main pancreatic duct was defined as "essential" in the Korean diagnostic criteria [8]. More recently, some authors reported that AIP may be radiologically classified into focal and diffuse forms [9–11]. For the first time, a focal enlargement of the gland, "occasionally with a mass and/or hypo-attenuation rim," has been included as a possible form of AIP by the 2008 Joint Korean and Japanese Consensus [12]. A recent radiological review from the USA stressed that focal forms of AIP, designated as "atypical," represent up to 40% of AIP cases [13]. In a recent Italian series of 87 patients with AIP, the focal form occurred in 63% of patients [11].

From a clinical point of view, focal forms of AIP are of particular interest since they share many clinical and imaging features with pancreatic carcinoma, yet they have a benign course and can be easily managed conservatively using steroid therapy, resulting in dramatic improvements.

2. Epidemiology

AIP is thought to be a relatively rare condition, but its actual incidence and prevalence are still unknown. Since there is no international agreement about diagnostic criteria and no serological markers have yet been identified, it may be significantly underreported. AIP accounts for 4–6% of all chronic pancreatitis cases [14,15], and up to 23% of pancreatic resections for presumed malignancy are done for AIP [16]. Series conducted in Italy, Asia and the USA obtained somewhat different epidemiological results, however the discrepancies are probably related to the different diagnostic criteria used and to the inclusion of focal forms of the disease in the Italian series [11–16].

Patient age varies widely (30–70 years), but most are older than 50 years. AIP affects men more often than women (ratio 2:1) [14].

Association with other autoimmune diseases, particularly of the gastrointestinal tract, seems to be quite common. In particular, ulcerative colitis represented up to 30% of the associated

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1590-8658/$36.00
doi:10.1016/j.dld.2009.08.006

autoimmune diseases in an Italian series [14]. The association between AIP and ulcerative colitis has been further confirmed in a recent USA study [17]. However, it is still unclear whether autoimmune diseases represent only an association or if they are an extrapancreatic manifestation of a systemic autoimmune process that is possibly IgG4-mediated.

3. Etiopathogenesis and laboratory findings

The term AIP was introduced solely because of the condition's dramatic response to steroid therapy. However, autoimmune pathogenesis has not yet been demonstrated since specific autoantibodies have not yet been discovered. Some serological features of autoimmunity may be present in AIP, but they are not specific for the disease.

Similarly to other autoimmune diseases, in the Japanese population a relationship with the HLA haplotype DRB1*0405–DQB1*0401 HLA has been reported [18]. Currently, elevated serum IgG4 levels are considered to be the sole serological hallmark of AIP. Hamano et al. found that serum IgG4 levels were significantly higher in patients with AIP than in healthy subjects. By contrast, in patients with pancreatic cancer and chronic pancreatitis, serum IgG4 levels were similar to those of normal subjects [19].

After this initial report, many other papers have been published on the diagnostic value of serum IgG4 in AIP. However, they report lower sensitivity and specificity [20–23]. In particular, Ghazale et al. confirmed that serum IgG4 are elevated in AIP, but they also underlined that 10% of patients with pancreatic cancer may have a non-specific increase in serum IgG4 (<2-fold) [20]. Using a >140 mg/dL cut-off, similar to that used by Hamano et al., these authors reported a sensitivity of 76%, a specificity of 93% and a positive predictive value (PPV) of only 36%. Using a higher cut-off (280 mg/dL), the specificity and PPV increased (99% and 75%, respectively), but the sensitivity was only 53% [20]. A recent meta-analysis confirmed that serum IgG4 may be useful as an AIP marker, but the heterogeneity of the published studies do not permit an assessment of the real accuracy of the test [23]. Further studies are necessary to evaluate the exact value of IgG4 for discriminating AIP from other autoimmune diseases and pancreatic cancer.

Additional serological markers of AIP are autoantibodies against lactoferrin and carbonic anhydrase II, and these are found in most of the organs involved in the systemic form of AIP [24]. However, these antibodies, often found in AIP patients at low titre, seem to be non-specific.

4. Clinical features

Up to 70–80% of patients present with painless jaundice. This may be related to the focal form of the disease involving the pancreatic head, or to biliary involvement by the autoimmune process. Acute pancreatitis is also frequently observed in these patients, but severe acute pain is rare and necrotising pancreatitis has never been reported in the literature [11,16,25]. Symptoms related to endocrine (diabetes, weight loss) and exocrine (steatorrhea, weight loss) insufficiencies may also be observed [26,27]. The presence of a pancreatic mass, the onset of diabetes and significant weight loss lead to a possible diagnosis of pancreatic cancer. Even in the face of negative findings by cytology or biopsy, these patients (particularly older patients) often undergo pancreatic surgery, because neoplasia cannot be excluded. The symptoms are different in focal and diffuse forms of the disease. Jaundice is more frequent in the focal form, whereas pancreatitis is more frequently observed in the diffuse form [14]. If the patient has a previous history of autoimmune disease, this helps in the identification of the disease, particularly in young subjects.

The biliary tree, gallbladder, kidney, lung, and salivary glands can be involved in the systemic form. Extrapancreatic symptoms are related to intra- or extra-hepatic biliary strictures, hydronephrosis due to retroperitoneal fibrosis, interstitial nephritis, interstitial pneumonia, mediastinal lymphadenopathies and sicca syndrome. These conditions may represent the clinical onset of the disease [15,28–33]. AIP may be associated with inflammatory bowel disease, particularly ulcerative colitis [14,17,34]. Most of the symptoms improve with steroid therapy, and spontaneous remission has also been described [35].

5. Histological features

From a pathological point of view, AIP may be considered a unique form of pancreatitis [14]. Upon gross examination, the pancreas can appear diffusely or focally hardened. If focally involved, the mass cannot be distinguished from pancreatic cancer. A histological hallmark of AIP is peri-ductal infiltration by inflammatory cells (lymphocytes and plasma cells) with diffuse fibrosis often arranged in a storiform pattern and obliterative phlebitis [34]. The lymphocytes are CD4+ and CD8+ T cells, whereas B lymphocytes are less commonly observed [34].

AIP can be pathologically classified into (1) a prevalent inflammatory form, designated "idiopathic duct-centric chronic pancreatitis (IDCP)" by Notohara et al. [36] and "AIP with granulocyte epithelial lesion (GEL)" by Zamboni et al. [34]; and (2) a prevalent sclerosing form, called lymphoplasmacytic sclerosing pancreatitis [5,36]. The relationship between these forms is not understood. Zamboni et al. stressed that GEL+ AIP is more frequently associated with ulcerative colitis and seems to relapse less frequently after steroid treatment [34].

The diagnosis of AIP may be performed with surgical specimens. However, guided biopsies with either histological or cytological sampling may be diagnostic. A pathological hallmark of AIP is the presence of IgG4+ plasma cells both in the pancreas and in extrapancreatic tissues [37,38]. Recently, Kamisawa observed significant infiltration of IgG4+ plasma cells in the major duodenal papilla of patients with pancreatic head involvement and rare IgG4+ plasma cells in patients with pancreatic cancer, body or tail AIP and papillitis [39]. However, as observed for serum IgG4, IgG4+ plasma cells in pancreatic tissue do not represent a specific marker for AIP, since they are also observed in pancreatic cancer and in non-AIP chronic pancreatitis. The cut-off to define tissue positive for IgG4+ plasma cells with immunostaining of pancreatic lymphoplasmacytic infiltrate varies in pathological studies, ranging from 10 to 30 per high-power field (HPF). Kojima et al. observed that IgG4+ plasma cells were detected in 72.5% of AIP cases and in 63.1% of non-AIP chronic pancreatitis cases [39], respectively. However, by using a cut-off of 20 cells per HPF, 50% of pancreatic specimens of AIP were positive, whilst none of the pancreatic cancer specimens were. It has been suggested that EUS guided biopsies plus immunohistochemical evaluation for IgG4+ plasma cells are the main diagnostic criteria for AIP [40].

6. Imaging findings

6.1. Sonography

The role of sonography in the diagnosis of autoimmune pancreatitis is not well established. Sonographic images of the pancreas are not specific and rarely diagnostic of autoimmune pancreatitis. Typical findings of diffuse autoimmune pancreatitis are hypoechoic pancreatic swelling with the main pancreatic duct compressed

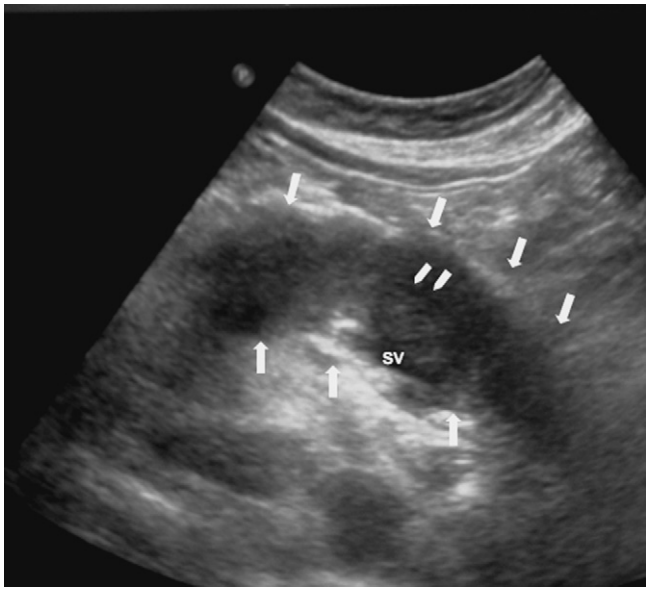

Fig. 1. AIP, diffuse form. Transverse epigastric US scan reveals a diffusely and substantially enlarged pancreas (arrows) with echo-poor echotexture and normal sized main pancreatic duct (arrowheads); SV = splenic vein.

by the parenchyma (Fig. 1). The focal form, commonly involving the head of the pancreas, can show single or multiple hypoechoic pancreatic masses, common bile duct dilatation, and less frequent upstream dilatation of the main pancreatic duct [41–43]. A recent report described sonographic findings of common bile duct wall thickening in 37 patients with AIP, making sonography a useful and non-invasive tool for the detection of biliary lesions [44].

Contrast-enhanced ultrasonography (CEUS) is evolving as a sensitive tool for evaluating the typical vascularisation pattern of autoimmune pancreatitis. Moreover, it may be a good indicator for monitoring the efficacy of steroid therapy [41,45]. In this setting, after injection of intravenous contrast agents, focal pancreatic lesions show enhancement in both the early and delayed phases with a slow washout. These enhancement patterns differ from pancreatic carcinoma and decrease after steroid treatment, as they are related to the degree of inflammation and inversely related to the fibrosis grade [45].

6.2. Computed tomography (CT)

The classical form of autoimmune pancreatitis in abdominal CT presents as diffuse pancreatic enlargement, the so-called "sausage-shaped" pancreas (Fig. 2). After injection of contrast medium, a moderate pancreatic enhancement, a capsule-like low-density rim and bile duct wall enhancement can be observed in the early phase. The late phase can show a delayed diffuse pancreatic enhancement with a persisting peripheral rim of hyper-attenuation [10,46,47].

The focal form (more often involving the head and/or the uncinate process) appears as a hypo-attenuating or iso-attenuating mass with a smooth contour in dynamic CT (Fig. 3).

Other findings suggestive of AIP are solid renal lesions and retroperitoneal fibrosis [48]. Enlarged peripancreatic lymph nodes can also be seen [49].

Pancreatic calcifications can be present but they are not typical for AIP [50]; cysts and pseudocysts are also uncommon. Pancreatic duct dilatation is possible in the focal forms [10], but its abrupt cut-off should suggest a pancreatic carcinoma. Vascular involvement is possible in both situations [48,49]. After steroid therapy, there is a normalisation of the pancreatic size and enhancement patterns (Fig. 4) [10]. However, in the case of long-standing autoimmune pancreatitis, CT can show pancreatic parenchymal atrophy.

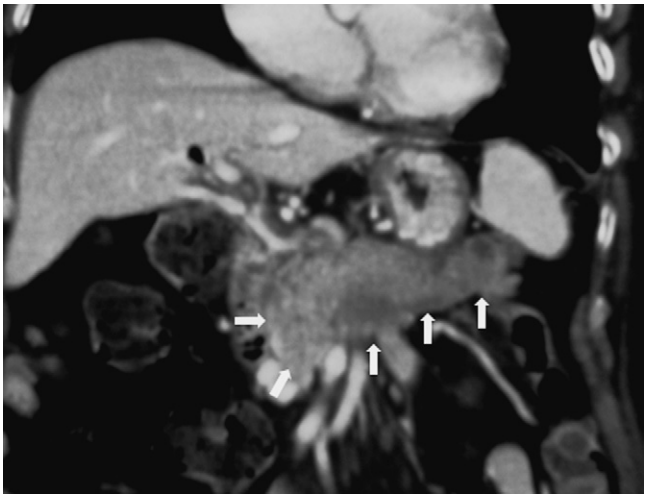

Fig. 2. AIP, diffuse form. Contrast-enhanced CT shows the diffuse pancreatic swelling (arrows).

6.3. Magnetic resonance (MR) and MR cholangio-pancreatography (MRCP)

MR imaging reveals focal or diffuse pancreatic enlargement that is hypo-intense in T1-weighted MR images and slightly hyper-intense in T2-weighted images. As with CT, a capsule-like hypo-intense rim can be observed in T2-weighted MR images [46]. As with endoscopic retrograde cholangio-pancreatography (ERCP), MRCP can show multiple intrahepatic strictures, dilated intrahepatic ducts and stricture of the common bile duct [49].

MRCP cannot visualise the narrow portion of the main pancreatic duct, but it can show the non-involved regions. For these reasons, MRCP cannot differentiate irregular narrowing of the main pancreatic duct from the stenosis typical of pancreatic carcinoma.

After steroid treatment, pancreatic size and signal intensity improves, the capsule-like rim disappears and the main pancreatic duct can be seen by MRCP. These findings suggest a role for MRCP in following patients on therapy, but not in diagnosing AIP [51].

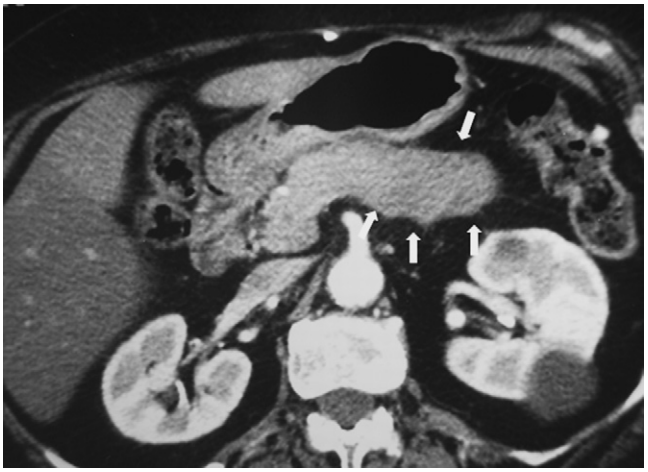

Fig. 3. AIP, focal form. Contrast-enhanced CT shows an enlarged pancreatic body and tail (arrows).

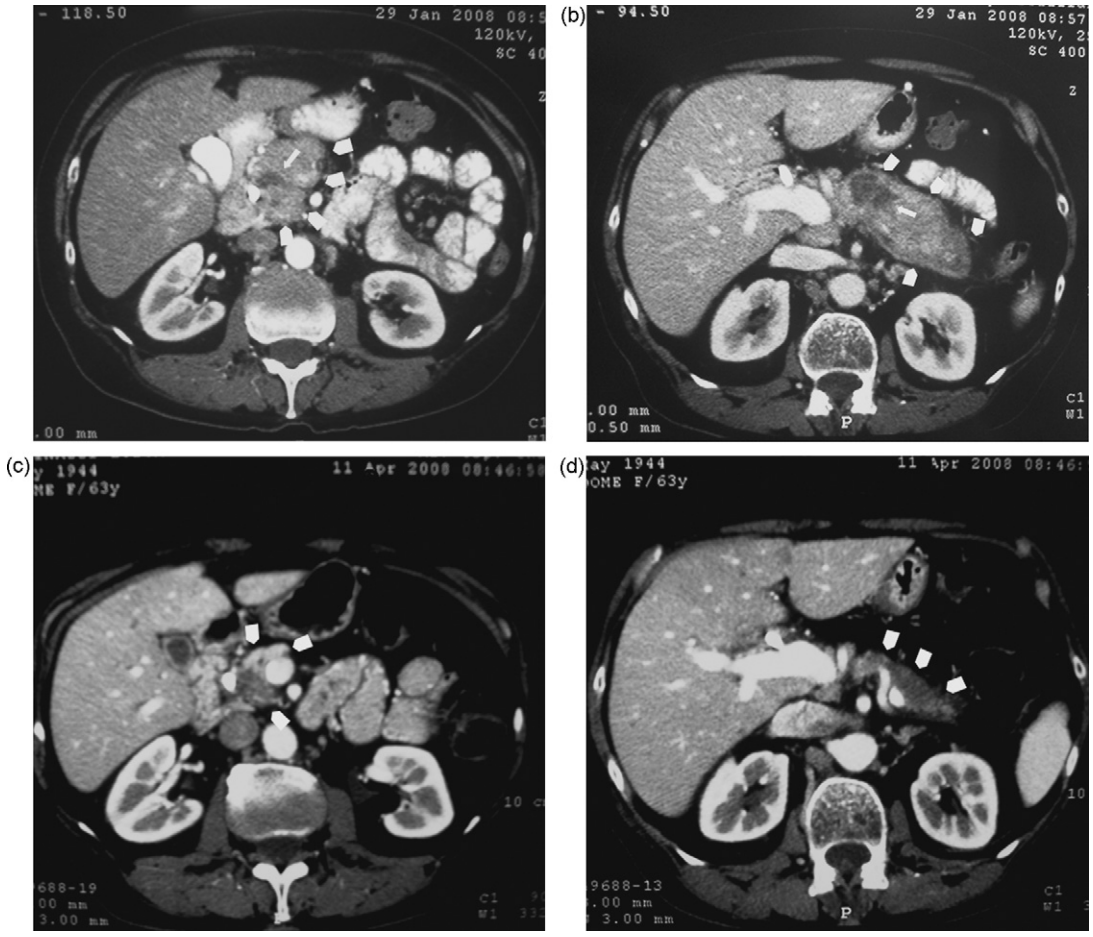

Fig. 4. A contrast-enhanced axial CT scan (a and b) shows that the pancreatic gland (arrowheads) is swollen with some hypodense areas (arrows). The CT check (c and d) after 6 weeks of steroid treatment shows the marked decrease in size of the gland, either head or body and tail (arrowheads).

6.4. 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) and PET/computed tomography (CT)

Little data is available concerning the role of FDG-PET and PET/CT in AIP characterisation. Nakajio et al. carried out FDG-PET and PET/TC studies on six patients with AIP suspected of having pancreatic cancer. They reported an intense FDG pancreatic uptake in all patients that disappeared after steroid therapy. Moreover, five patients had associated extrapancreatic lesions, and these showed the same FDG uptake as the pancreas [52]. Unfortunately, FDG-PET and PET/CT cannot differentiate the FDG uptake of AIP from that of pancreatic cancer, but they may be useful for detecting AIP lesions and monitoring disease activity after steroid therapy.

6.5. Endoscopic retrograde cholangio-pancreatography (ERCP)

One of the diagnostic criteria for AIP is a diffuse or segmental narrowing of the main pancreatic duct with irregular wall in ERCP. This finding, in association with stenosis of the intrapancreatic common bile duct (Fig. 5), represents the ERCP hallmark of AIP.

In the focal form, the main pancreatic duct can be dilated adjacent to or upstream of the strictures; if this pattern coexists with low common bile duct stenosis, it can resemble the double-duct sign typical of pancreatic carcinoma.

Other common ERCP characteristics are irregular narrowing of the hilar hepatic region, and less frequently, segmental intrahepatic bile duct strictures [53].

The latter cholangiographic finding can mimic primary sclerosing cholangitis.

ERCP also has a therapeutic role, allowing biliary drainage and stent placement, although the response to steroids improves the pancreatic duct changes and (to a lesser degree) the biliary changes.

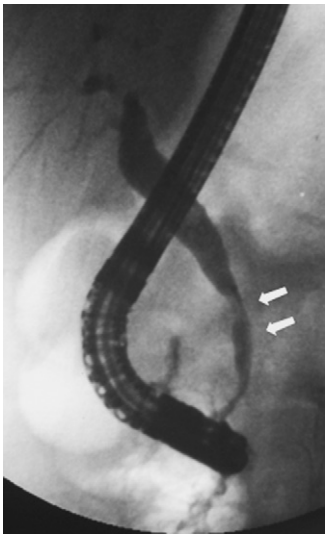

Fig. 5. AIP, with common bile duct involvement: endoscopic retrograde cholangiography shows a stenosis of the distal common bile duct (arrows).

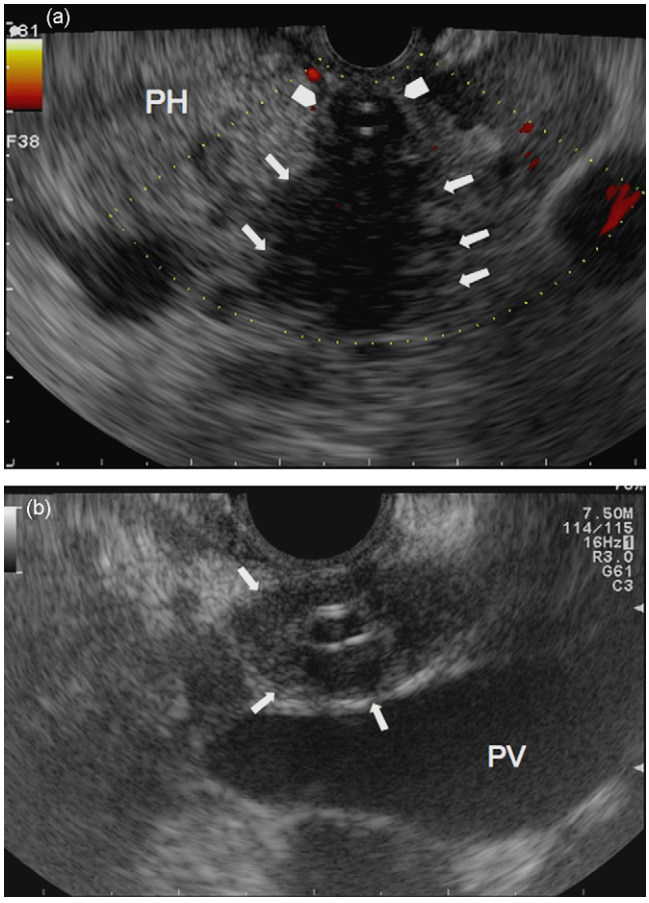

Fig. 6. Linear EUS (a) shows a focal roundish echo-poor lesion (arrows) in the pancreatic head (PH), and the common bile duct (arrowheads) has a diffusely thickened wall. The bile duct wall thickening (arrows) (b) has a "sandwich-pattern", with an intermediate echo-poor layer and echo-rich inner and outer layers. PV = portal vein.

However, biliary strictures can progress even with steroids and require long-term treatment [6].

6.6. Endoscopic ultrasonography (EUS)

EUS is superior to CT, MR and ERCP for detecting small pancreatic masses, and its role in the diagnosis of AIP is enhanced by the possibility of an effective and safe pancreatic biopsy [54,55].

EUS features of AIP are a diffusely hypoechoic pancreatic swelling and/or a hypoechoic mass in the head of the pancreas (Fig. 6). Another finding suggestive of AIP is common bile duct dilatation with a thickened wall [56,57]. The thickening of the bile duct wall in AIP shows some unique features: it is homogeneous, with an echo-poor intermediate layer and hyper-echoic outer and inner layers and a "sandwich-pattern" wall that may reach 5 mm in thickness (Fig. 6). Differentiation of biliary involvement from biliary or pancreatic carcinoma is based on the presence (in the latter cases) of irregular echo-poor lesions transmurally involving the duct wall.

Hyodo et al. performed contrast-enhanced EUS of the bile duct in AIP, and it showed early enhancement of the bile duct wall that was different from the poor enhancement of cholangiocarcinoma. The enhancement was reduced after steroid treatment [57].

Main pancreatic duct dilatation is possible in the focal form, whereas it is compressed by the enlarged parenchyma in the diffuse form of AIP [56].

Vascular involvement of the portal and/or superior mesenteric vein has been reported and should not preclude the diagnosis of AIP, because the inflammatory infiltrate can transmurally involve the vessel walls determining the EUS finding of invasion [56].

Single or multiple enlarged peripancreatic and celiac lymph nodes can also be detected that are reflective of the inflammatory process.

Even if EUS-FNA is sensitive and specific for the diagnosis of pancreatic malignancy, the cytopathologic diagnosis of AIP is not standardised. EUS fine-needle aspiration (FNA) of pancreatic masses, lymph nodes and the common bile duct wall can reveal fibrosis and lymphoplasmacytic infiltrate, and EUS-FNA findings correlate well with surgical pathologic diagnosis [56]. However, it is difficult to obtain sufficient pancreatic tissue to achieve a definitive diagnosis without a laparotomy, and sampling error is possible since the disease has a patchy distribution. It has been proposed that a cytologic smear with stromal fragments rich in inflammatory cells and epithelial cells lacking atypia is diagnostic of AIP [58]. EUS-guided Tru-cut biopsy (EUS-TCB) with a 19-gauge needle acquires larger tissue specimens whilst preserving tissue architecture and this may allow for histological confirmation and prevent unnecessary surgery [40].

7. Diagnostic criteria

Taken together, these considerations suggest that the only pathognomonic criteria that can be used to definitively diagnose AIP are those requiring a surgical specimen. In practice, the diagnosis usually results either from surgical over-treatment or a combination of different features that together make the diagnosis reliable. Thus far, there is no consensus on the minimal diagnostic criteria for AIP. Current AIP diagnosis is based on criteria proposed by the Japan Pancreas Society in 2002 and revised in 2006 [7,59]. According to these criteria, specific imaging, serological and histological criteria must be fulfilled in order to make a diagnosis of AIP. The Korean criteria of response to steroids and extrapancreatic lesions supplement the Japanese criteria [60]. In 2008, a Japan–Korea Symposium incorporated the previous criteria into the new Asian diagnostic criteria for AIP [12]. The Mayo Clinic proposed criteria for AIP (termed HISORt) in 2006 focus on histological features, and these are considered to be the gold standard [61]. Italian investigators proposed the use of a combination of histological and cytological findings, including association with other autoimmune diseases and response to steroid therapy [11]. These diagnostic criteria are listed in Table 1.

In summary, the main diagnostic criteria in Asia are based on radiological and serological findings, whilst in the USA diagnosis is based on disease pathology. In Italy, the primary accepted criterion (if biopsies are not diagnostic for the disease) is the response to steroids, but this should be used only if clinical, pathological and radiological data are consistent with AIP and pancreatic cancer can be confidently excluded.

The existence of so many diagnostic criteria underlines the difficulty of preoperative AIP diagnosis, and in particular the difficulty of differentiating it from pancreatic cancer. Appropriate diagnostic criteria are still under debate and International Consensus Criteria are awaited. Both the lack of defined guidelines and the risk of misdiagnosed pancreatic cancer underscore how important it is for AIP patients to be managed in experienced centres.

8. Therapy

Steroid drugs are standard therapy, although spontaneous resolutions have also been described [35]. However, a therapeutic schedule has not yet been standardised. Usually therapy starts with 30–40 mg prednisone daily for 1 week, but higher dosages

Table 1
Diagnostic criteria for autoimmune pancreatitis.

Asian Criteria [12]
- Criterion I. Imaging (both required)
  1. Imaging of pancreatic parenchyma: diffuse/segmental/focal enlargement of the gland, occasionally with a mass and/or hypoattenuation rim
  2. Imaging of pancreaticobiliary ducts: diffuse/segmental/focal pancreatic ductal narrowing, often with the stenosis of the bile duct
- Criterion II. Serology (one required)
  1. High levels of serum IgG or IgG4
  2. Detection of autoantibodies
- Criterion III. Histopathology of pancreatic biopsy lesions
- Lymphoplasmacytic infiltration with fibrosis, with abundant IgG4-positive cell infiltration
- Optional criterion: Response to steroid therapy.
- Diagnosis is established when criterion I and one of the other two criteria are satisfied, or when the histology shows the presence of lymphoplasmacytic sclerosing pancreatitis in the resected pancreas

HISORt Criteria [61]
- Histology (at least one of the following):
  1. Peri-ductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis
  2. Lymphoplasmacytic infiltrate with storiform fibrosis showing abundant (10 cells/HPF) IgG4-positive cells
- Pancreatic imaging
  1. Typical: diffusely enlarged gland with delayed enhancement; diffusely irregular, attenuated main pancreatic duct.
  2. Others: focal pancreatic mass/enlargement; focal pancreatic duct stricture; pancreatic atrophy; pancreatic calcification; or pancreatitis
- Serology
  - Elevated serum IgG4 level
- Other organ involvement
  - Hilar/intrahepatic biliary strictures, persistent distal biliary stricture, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis
- Response to steroid therapy
  - Resolution/marked improvement of pancreatic/extrapancreatic manifestation with steroid therapy
- Diagnosis is established when one histologic criterion, typical imaging criteria, serologic and response to steroid criteria are satisfied.

Italian Criteria [11]
- In non-operated patients, 3 of the 4 following criteria:
  1. Histology or cytology that should exclude pancreatic cancer and may reveal the presence of granulocyte epithelial lesion
  2. Suggestive radiological findings
  3. Association with other autoimmune diseases or extrapancreatic involvement
  4. Response to steroid therapy
- In operated patients: pathology in surgical specimens

may be used (1 mg/kg/day) [11]. After 2–3 weeks, the steroids may be tapered by 5 mg/week till withdrawal. Symptoms usually improve rapidly within the first week of treatment [62,63]. The onset of diabetes or its worsening may be observed within the first week of steroid treatment, but glucose balance improves thereafter, probably due to the reduction of pancreatic inflammation. Furthermore, laboratory results and IgG4 levels normalise and imaging abnormalities improve (Fig. 4). A control imaging study is recommended after 3–4 weeks of therapy [11,63]. A poor response to steroids could suggest another underlying disease, and if the diagnosis of cancer cannot be safely excluded, surgery is mandatory.

Relapses occur in 6–54% of patients [11,53,62–65], and recurrences seem to be more frequent in focal AIP than in diffuse AIP [11]. Serological relapse with elevated IgG4 has been described, but its role in disease evolution is not clear [66]. Patients with biliary strictures improve slowly and relapse is more common; therefore, a tailored therapy should be attempted in these cases [63,65].

Relapse is usually treated with a second course of steroids, but some cases require long-term maintenance therapy with a low steroid dose (5–10 mg daily) [40]. Steroid-sparing immunosuppressive drugs have been recently suggested [67].

9. Conclusion

AIP is a rare disease with a benign course, but distinguishing it from pancreatic cancer remains difficult despite progress in diagnostic imaging. A definitive AIP diagnosis requires a multidisciplinary approach and specialists experienced in pancreatic disease. In patients with clinical history and symptoms suggestive of AIP and a focal pancreatic mass, pancreatic cancer should be ruled out. EUS-FNA or EUS-TCB is necessary in these cases to obtain pancreatic tissue. Immunostaining for IgG4 plasma cells may represent a further diagnostic tool to reach the diagnosis and to exclude pancreatic cancer.

Patients without a definite pathological diagnosis of AIP should be evaluated in tertiary centres with expertise in the field. If clinical history, imaging and serological data are consistent with AIP, a trial with steroids can be used as a diagnostic criterion, provided that a strict radiological follow-up is scheduled.

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